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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,475	06/04/2001	Christos J. Petropoulos	2793/65166/JPW/JML/CMR	5338

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	11

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,475	PETROPOULOS ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 6, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of Group I in Paper No. 10 is acknowledged. The traversal is on the ground that the search of Groups I and II would not pose a serious burden to search. This is not found persuasive because Groups I and Group II utilize different method steps. Group I is an assay for identifying compounds that inhibit viral entry into a cell, while group II is a method of determining the resistance of a virus to a particular compound. Group II requires knowledge that the compound has a specific effect. The groups do not utilize the same stating materials and the outcomes of each method would not be expected to be the same. The requirement is still deemed proper and is therefore made FINAL.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be

incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicant is reminded of the proper format for incorporation by reference see MPEP 604.01(p). Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

Drawings

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action.

It is noted that figure 1 utilizes a color background in the figure when reproduced the figure is completely black and shows no information. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to composition that are speculated to exist and are screened for by the methods set out in the specification.

The specification has shown a method of screening for compounds that have a desired effect. The claims encompass a genus of compounds defined only by their function wherein the relationship between the structural features of members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Although the description does not provide working examples, the description teaches a method for measuring the biochemical and binding activity of envelope constructs and the

person skilled in the art can understand how to use the screening method considering the common general knowledge.

To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention Edith all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was Already for patenting" such as by the use of drawings or structural chemical formulas that show that the invention was complete, or describing distinguishing identifying characteristics sufficient to show that the applicant was in Possession of the claimed invention.

Claimed invention is drawn to an compositions and carriers identified by the method of claim 1. However, no structural or specific functional characteristics of such a compound is provided, nor is there any indication that the artisan actually implemented the method of claim 1 so as to identify any compounds. This situation is analogous to that of *Regents of the University of California v Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention. The claim fails to comply with the written description requirement.

Claims 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to composition that are speculated to exist and are screened for by the methods set out in the specification.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. Such an analysis does not need to specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection.

The specification has shown a method of screening for compounds that have a desired effect. A claim meets the utility requirement of 35 U.S.C. § 101. Only one specific, substantial, and credible utility is required to support the requirements of 35 U.S.C. § 101. In the instant cased the presence or absence of the of the envelope construct to bind to a cell surface receptor is useful in diagnostic methods relating to HIV virulence.

Claim 1 meets the enablement requirement for the "how to use" prong of 35 U.S.C. § 112, first paragraph because the specification provides guidance regarding the screening method. However, this claim does not meet the requirement for the "how to make" prong of 35 U.S.C. § 112, first paragraph because there is no disclosed structure that would meet the utility

requirement of 35 U.S.C. § 101 (see utility discussion, above). The instant fact pattern fails to disclose any particular structure for the claimed composition. The specification does not provide any guidance or any working examples in this unpredictable art, and thus the artisan would have been unable to have prepared the claimed composition without undue experimentation. Furthermore an assay for finding a product is not equivalent to a positive recitation of how to make such a product. This claim fails to meet the enablement requirement for the "how to make" prong of 35 U.S.C. § 112 first paragraph.

While the claimed compound meets the utility requirement of 35 U.S.C. § 101 the claimed invention does not comply with the "how to use" prong of 35 U.S.C. § 112, first paragraph. The specification does not teach how to administer the claimed composition so as to effect a viable treatment regimen. Treatment/administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the subject or patient. In the absence of additional information the skilled artisan would not have been able to use the undisclosed compound(s) for treatment without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-28 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al. (Journal of Virology, 1996) and Petropoulos et al. (Antimicrobial Agents and Chemotherapy, April 2000) in view of Grovit-Ferbas et al. (Journal of Virology, 1998) and Trkola et al. (Journal of Virology, 1999)

The instant claims are drawn to a method of identifying a compound that inhibits viral entry into a cell. The method comprises taking a sample from a patient and extracting the nucleic acid sequence of a viral envelope protein, specifically HIV (claim 7 and 8). "Comprising" is a term of art used in claim language that means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. This patient derived nucleic acid sequence in conjunction with an indicator vector is transfected into a cell. The indicator vector comprises HIV nucleic acid sequences (claims 9-11). The transfected cell is able to produce viral particles, the cells can be mammalian, human, human embryonic kidney cells or 293 cells (claims 12-15). These particles are then tested for their ability to enter into a new cell (see claims 16-22) in the presence of a suspected inhibitory compound. If the cells are infected with the particles they will produce a signal, which can be measured against viral entry in the absence of the suspected compound. The signal can be

produced from the luciferase gene (claim 3). The cell surface receptors that can be tested are CD4, chemokine receptors, CXCR4, CCR5. The inhibitory compound binds to cell surface receptors, can be antibody or ligand to cell surface receptor and prevent membrane fusion (claims 23-28).

Gao et al. teaches the use of single round virus infectivity assay utilizing patient derived amplified *env* segments. In this assay the patient derived *env* gene pSVIII-gp160 constructs which expressed functional envelope under the control of HIV-1 long terminal repeat promoter. pSVIII-gp160 were co-transfected with HXBH10Δenv CAT into Cos-cells. HXBH10Δenv CAT is an *env* deficient provirus, which contains a chloramphenicol actyltransferase (CAT) gene in place of the *nef* gene. After culturing in the Cos cells the produced virions are collected and used to infect new donor derived peripheral blood mononuclear cells (PBMC), the cells were then assayed for the presence of CAT activity (see page 1654, material and methods). The proposed utility for the generated envelope clones includes the use of the constructs for the analysis of fusion enhancement *env* complementation and infectivity assays (see page 1665, last paragraph). The assay disclosed in the reference utilizes obtaining a nucleic acid sequence into pSVIII-gp160. Co-transfecting a cell (Cos cells) with a viral expression vector and the viral envelop sequence, collecting the particles produced from the cell and contacting the viral particle with PBMC, measuring the amount of signal produced (CAT). Though the reference suggest the use of these envelope constructs for studying infectivity the reference did not disclose a step-by-step assay to assay a compound for the ability to inhibit viral entry into a permissive cell.

Grovit-Ferbas et al. teach the production of chimeric full-length viruses in which patient derived *env* segments are inserted into the virus. These viruses are than assayed for their co-

receptor usage (see material and methods) the osteosarcoma cells expressing CD4 and one of the following chemokine receptors: CCR1, CCR2, CCR3, CCR4, CCr5, GPR15 (BONZO), STRL33 (BOB) or CXCR4. The reference teaches a cell line that can be modified with various co-receptors and that each patient sample must be assayed for the ability to utilize the various correctors for entry. The differences in replication kinetic is linked to the efficiency of viral entry. The premise of the study is that genetic differences in viral envelope sequences which result in inefficient entry into cells may be important determinants in long-term survival. The study specifically looks at identifying viral isolates with their respective coreceptor usage. The reference does not teach assaying compounds for their ability to interfere with viral entry.

Petropoulos et al. teach a single cycle transfection assay with HIV vectors in which a patient sample can be tested for the sensitivity to a compound. In this sassy the patient derived sample involves the HIV polymerase gene. The reference discloses a resistance test vector that contains *gag-pol* but has the envelope region deleted and the luciferase reporter gene inserted instead, this is referred to as the resistance test vector. The reference uses an amphotropic MLV *env* DNA segment that is on a second vector, which will produce particles that have a reduced risk of recombination event for producing fully infectious HIV particles (see page 922, figure1). This assay set up reduces the risk to laboratory personal. The reference teaches an assay that tests for the effectiveness of compounds and their ability to inhibit HIV replication. The assay allows for monitoring the frequency of drug resistance virus transformation in a patient sample. The assay can be used to screen for new drugs that are active against HIV resistant strains (see page 926, last paragraph). The reference does not teach analyzing patient derived HIV *env* segment for their ability to infect new cells and for compounds that may inhibit the viral entry.

Trkola et al. teach the use of antibodies as a compound for inhibiting the entry of a viral particle into a host cell. The reference teaches the use of neutralization assay for the analysis of primary HIV-1 isolates. The reference does not teach analyzing amplified *env* segments from patient derived samples for their ability to be inhibited by antibodies.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to test a patient derived HIV sample for the ability to be inhibited by a compound that will prevent viral entry. One having ordinary skill in the art would have been motivated to do this in order to develop a drug regime that is specific for the patient. By determining if the patient derived virus has mutated in such a way as to be resistant to the drug regime that the patient is being treated with, it would have been obvious to one having ordinary skill in the art to monitor antiretroviral therapies. This information is clinically valuable by providing reliable assessment of the viral burden and is useful in monitory the clinical efficacy of the treatment. Gao et al. teach a single round infectivity assay that utilizes various patient derived and amplified *env* segments, the reference utilizes CAT as the indicator gene which is found on the resistance test vector which also comprises the *gagpol* gene sequences but has the *env* sequence deleted. The reference teaches that different *env* sequences have different biological characteristics. The *env* clones can be utilized in envelope complementation and infectivity assays. Petropoulos et al. teach an assay for testing drug susceptibility, the assay utilizes a resistance test vector comprising *gagpol* sequences and a *env* vector for the production of viral particles from cotransfected cells. Grovit-Ferbas et al. teach that different viral envelope sequences have different effects on the ability of a viral particle to enter a host cell. Those viruses that have diminished capacity to enter a new host cell are found in long term HIV survivors, indicating that

reducing the ability of a new particle to enter the next host cell will be beneficial for increasing the survival of an HIV infected person. The reference also teaches assaying each viral envelope sequence for the usage of different coreceptors. While the Trkola et al. reference teaches an assay that determines if an antibody is able to inhibit the entry of a viral particle into a new host cell. The prior art teaches assays that focus on the HIV viral envelope protein and indicate preventing viral entry by blocking the association of the viral envelope with the cell surface receptor is desirable drug target. It is well established in the prior art that HIV has a high mutation rate, especially in the envelope region, hence vaccines have not been successful due to the changing envelope structure of the virus. The prior art also indicated that for any therapy to be effective it is necessary to assay the changes in the virus population in a patient and follow the mutations that occurs when applying drug therapy. This will ensure that the patient is treated with the best possible drug combination that is effective for the virus the patient harbors at any point. Therefore, the instant invention is obvious over Gao et al. and Petropoulos et al. in view of Grovit-Ferbas et al. and Trkola et al.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Paulous et al. U.S. Pat. No. 6,103,462.

Capon et al. U.S. Pat. No. 6,242,187 B1.

Helseth et al. Rapid Complementation assays measuring replicative potential of human immunodeficiency virus type-1 envelope glycoprotein mutants. Journal of Virology (1990), Vol. 64, No. 5, pages 2416-2420.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 1/27/03